Does Sepsis-Associated Encephalopathy Begin and End with T Cells?

Masafumi Saito*

Department of Disaster and Emergency and Critical Care Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

***Corresponding author**: Dr. Masafumi Saito, Department of Disaster and Emergency and Critical Care Medicine, Kobe University Graduate School of Medicine, Kusunoki-Cho 7-5-2, Chuo-Ward, Kobe, Japan, Tel: +81-78-382-6521; Fax: +81-78-341-5254; E-mail: msaito@med.kobe-u.ac.jp

Received date: October 12, 2021; **Accepted date:** October 26, 2021; **Published date:** November 02, 2021

Literature Review

Attenuation and alleviation of SAE and mental impairment

In a septic mouse model, sepsis-induced anxiety-like behaviours naturally recovered within approximately two months [31-40]. Surprisingly, an increase in the number of microglia was observed during this time. In fact, this increase was observed for at least 90 days following sepsis induction [32]. Microglia expresses a wide variety of receptors on their cell surface, one of which is the fractalkine receptor CX3CR1 (C-X3-C motif chemokine receptor 1). Expressed/unexpressed phenotype of microglia is involved in the development of mental impairment in mice. CX3CR1- microglia increased in the brains of mice following lipopolysaccharide (LPS)-induced endotoxin shock [41]. Moreover, CX3CR1-/- mice showed prolonged anxiety behavior following LPS administration [41]. With regards to sepsis, we observed an increase in the number of CX3CR1- microglia in the brains of septic mice, with the phenotype decreasing gradually with the alleviation of anxiety-like behaviours (unpublished data). These results suggest that it is essential to investigate the phenotype of microglia after the onset of sepsis, and to clarify how CX3CR1+ microglia are involved in the alleviation of mental impairments. The role of astrocytes in the recovery process of SAEs and mental impairment, however, is not well elucidated. In a previous study, we showed that astrocyte levels return to baseline levels in the chronic phase after an initial drop in the acute phase of sepsis [33]. How this recovery takes place, however, remains unclear.

Discussion

Interestingly, T cells (especially CD4+ T cells) in the brains of septic mice increased for at least 30 days following sepsis induction [33]. This observation prompted us to investigate whether it plays a role in the alleviation of mental impairment following sepsis. To test this, we treated septic mice with FTY720 to inhibit the infiltration of lymphocytes into the brain. This resulted in recovery from anxiety-behaviour being delayed in FTY720-treated septic mice. Moreover, FTY720-treated septic mice showed notably high mRNA levels of Il-1β and tumor necrosis factor-α in the brain even 30 days after the onset of sepsis. More importantly, we observed an increase in the number of CX3CR1- microglia and a reduction of astrocytes in treated mice, suggesting that infiltrated CD4+ T cells in the brain are involved in the alleviation of mental impairments *via* an anti-inflammatory response. Finally, we confirmed our phenotypic observations using flow cytometry, and found an increase in Th2 and Tregs cells in the brain after sepsis [33]. Collectively, increased levels of Th2 and Tregs cells, in the brain contributed to the attenuation of SAE and alleviation of mental impairment during the chronic phase of sepsis, *via* recovery of brain homeostasis, by resolving the imbalance of astrocytes and microglia [42,43].

Conclusion and Future Work

Our study showed that infiltration of Treg and Th2 cells in the brain is critical for the attenuation of SAE and alleviation of mental impairment. These results could contribute to the improvement of long-term prognosis and quality of life for sepsis survivors after their discharge from the hospital. It is important to determine the source of these T cells. Since the BBB might have been repaired during the chronic phase of sepsis, it is difficult to conceive of how T cells are circulating in the blood and infiltrating the brain. Anatomical studies have shown that the draining lymph nodes of the brain are superficial cervical lymph nodes (CLNs), deep CLNs, and meningeal lymph nodes (MenLNs). Clarifying the circulation of T cells in the axis of Brain-CLN-MenLN under sepsis conditions would be the first step in the treatment of SAE.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, et al. (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315(8):801-810.
2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, et al. (2017) Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43(3):304-377.
3. Zachary M, Abraham P, Matthew M, Syed FM, Barbara L, et al. (2020) Post-sepsis syndrome - an evolving entity that afflicts survivors of sepsis. Mol Med 26(1):6.
4. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, et al. (2020) Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. Lancet 395(10219): 200-211.
5. Prescott HC, Langa KM, Iwashyna TJ (2015) Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. JAMA 313(10):1055-1057.
6. Gofton TE, Young GB (2012) Sepsis-associated encephalopathy. Nat Rev Neurol 8(10):557-566.
7. Peidaee E, Sheybani F, Naderi H, Khosravi N, Jabbari-Nooghabi M (2018) The etiological spectrum of febrile encephalopathy in adult patients: A cross-sectional study from a developing country. Emerg Med Int 2018:3587014.
8. Schuler A, Wulf DA, Lu Y, Iwashyna TJ, Escobar GJ, et al. (2018) The Impact of acute organ dysfunction on long-term survival in sepsis. Crit Care Med 46(6):843-849.
9. Yende S, Austin S, Rhodes A, Finfer S, Opal S, et al. (2016) Long-term quality of life among survivors of severe sepsis: analyses of two international trials. Crit Care Med 44(8):1461-1467.
10. Lemstra AW, Woud JCMG, Hoozemans JJM, Van Haastert ES, Rozemuller AJM, et al. (2007) Microglia activation in sepsis: a case-control study. J Neuroinflammation 15(4):1-8.
11. Bedirli N, Bagriacik EU, Yilmaz G, Ozkose Z, Kavutçu M, et al. (2018) Sevoflurane exerts brain-protective effects against sepsis-associated encephalopathy and memory impairment through caspase 3/9 and Bax/Bcl signaling pathway in a rat model of sepsis. J Int Med Res 46(7): 2828-2842.
12. Haileselassie B, Joshi AU, Minhas PS, Mukherjee R, Andreasson KI, et al. (2020) Mitochondrial dysfunction mediated through dynamin-related protein 1 (Drp1) propagates impairment in blood brain barrier in septic encephalopathy. J Neuroinflammation 17(1):36.
13. Shulyatnikova T, Verkhratsky A (2019) Astroglia in sepsis associated encephalopathy. Neurochem Res 45(1):83-99.
14. Hoogland ICM, Houbolt C, van Westerloo DJ, van Gool WA, van de Beek D. (2015) Systemic inflammation and microglial activation: systematic review of animal experiments. J Neuroinflammation 12(1): 1-13.
15. Danielski LG, Della GA, Badawy M, Barichello T, Quevedo J, et al. (2018) Brain barrier breakdown as a cause and consequence of neuroinflammation in sepsis. Mol Neurobiol 55(2):1045-1053.
16. Moraes CA, Zaverucha-do-Valle C, Fleurance R, Sharshar T, Bozza FA, et al. (2021) Neuroinflammation in Sepsis: molecular pathways of microglia activation. Pharmaceuticals (Basel) 14(5):416.
17. Liu J, Liu L, Wang X, Jiang R, Bai Q, et al. (2021) Microglia: A double-edged sword in intracerebral hemorrhage from basic mechanisms to clinical research. Front Immunol 12:675-660.
18. Miller SJ (2018) Astrocyte Heterogeneity in the Adult Central Nervous System. Front Cell Neurosci 12: 401.

19. V